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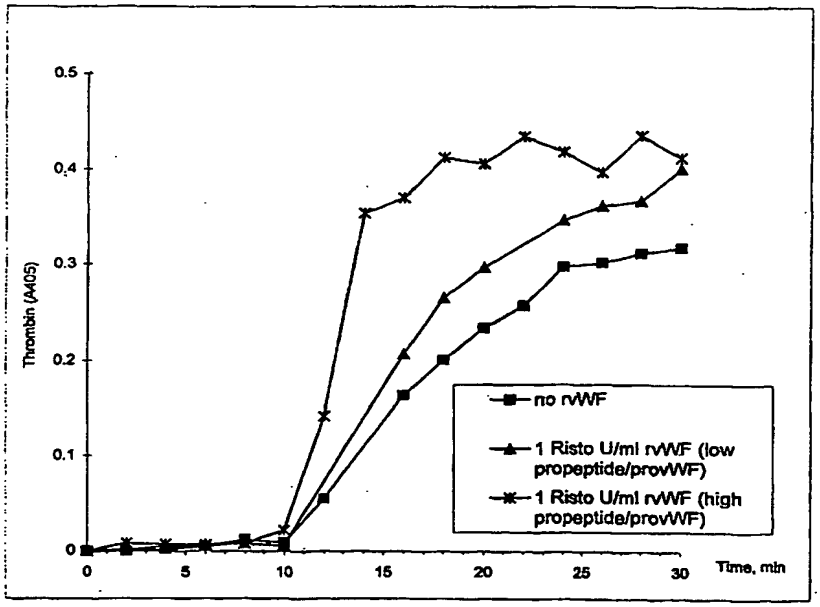
The effect of provWF on the thrombin generation in plasma in the presence of platelets.



(57) Abstract

Described is a pharmaceutical preparation for treating blood coagulation disorders comprising an effective amount of vWf propeptide as well as a method for producing such a prepartion.

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Pharmaceutical Preparation Comprising vWF Propeptide

The invention relates to a pharmaceutical preparation comprising the vWF-propeptide (pp-vWF).

Von Willebrand factor (vWF) is a glycoprotein circulating in plasma as a series of multimeres ranging in size from about 500 to 20 000 kD. Multimeric forms of vWF are composed of 250 kD polypeptide subunits linked together by disulfide bonds. vWF mediates the initial platelet adhesion to the sub-endothelium of the damaged vessel wall, only the larger multimers also exhibiting hemostatic activity. It is assumed that endothelial cells secret large polymeric forms of vWF and that those forms of vWF which have a low molecular weight (low molecular weight vWF) have arisen from proteolytic cleavage. The multimers having large molecular masses are stored in the Weibel-Pallade bodies of the endothelial cells and liberated upon stimulation.

vWF is synthesized by endothelial cells and megakaryocytes as prepro-vWF that consists to a large extent of repeated domains. Upon cleavage of the signal peptide pro-vWF dimerizes through disulfide linkages at its C-terminal region. The dimers serve as protomers for multimerization which is governed by disulfide linkages between the free end termini. The assembly to multimers is followed by the protelytic removal of the propeptide (Leyte et al., Biochem.J. 274 (1991), 257-261).

The full length of cDNA of vWF was cloned; the propolypeptide corresponds to amino acid residues 23 to 764 of the full length prepro-vWF (Eikenboom et al (1995) Haemophilia 1, 77-90).

The propeptide of vWF (pp-vWF) was shown to be identical to the von Willebrand antigen II, the second identified antigen that is deficient in the plasma and platelets of patients with severe von Willebrand disease (vWD). pp-vWF is specifically localized in platelets since plasma contains less than 5% of total propeptide vWF in blood, assuming the platelet count is 3 x 10^8 per ml. As already known, pp-vWF is released from platelets upon activation by various agonists. The pp-vWF is a glycoprotein not

only because it reacts with periodic acid Schiff's reagent but also because it binds to lentil lectin. pp-vWF binds specifically to native type I collagen, but does not bind to heat-denatured collagen. It was shown that the affinity between pp-vWF and type I collagen was quite high so that the binding - which does not require any divalent cation and is not affected by addition of a peptide that contains sequence of arginine-glycine-aspartic acid (that is known to inhibit many cell attachment processes) - rapidly reached equilibrium.

The physiological role of pp-vWF is postulated to lie in the government of the assembly of vWF multimers, either before or after the cleavage from pro-vWF molecules. (Takagi et al., JBC 264 (18) (1989), 10425-10430).

pp-vWF was also shown to inhibit the platelet collagen interaction action (Takagi et al., JBC 264(11) (1989), 6017-6020).

In Isobe et al. (JBC 272 (13) (1997), 6447-6453) the role of pp-vWF as a novel physiological ligand and an adhesion substrate for $\alpha 4\beta 1$ integrin-expressing leukemia cells was investigated. It was found that pp-vWF plays an important role in the mechanism underlying the melanoma metastasis as well as vascular inflammation.

Although pharmaceutical preparations containing mature vWF are known (see e.g. US 5,571,784) the pharmaceutical usage of pp-vWF or the pro-form vWF have not been described or suggested in the prior art. According to the US 5,571,784 vWF does not impair the systemic anticoagulatory effect of the anticoagulant hirudin as measured by the aPTT, rather it decreases the bleeding side effects of anticoagulant therapy. vWF is therefore proposed as a pseudo-antidote in assocation with hemorrhages which are produced by administering antithrombotic and/or fibrinolytic agents.

From Blann et al. (Eur.J.Vasc.Surg.8 (1994), 10-15) it is also known that vWF levels are increased with risk factors for

atherosclerosis and in patients with diffuse arterial disesase. The level of vWF is also thought to be a measure of endothelial $_4$>integrin-expressing leukemia cells was investigated. It was found that pp-vWF plays an important role in the mechanism underlying the melanoma metastasis as well as vascular inflammation.

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It is is the object of the present invention to provide a vWF pharmaceutic with improved properties. The preparation should enhance the intrinsic blood coagulation activity in individuals and reduce the arterial thrombotic risk of vWF therapy.

This object is solved by the present invention by providing a pharmaceutical preparation for treating blood coagulation disorders comprising an effective amount of vWF propeptide. It was found out that pp-vWF plays an essential role in blood coagulation. It promotes the intrinsic blood coagulation and thereby acts on secondary heostasis. At the same time it inhibits the platelet adhesion and controls the primary hemostatic activity of mature vWF by binding to collagen. Based

on these findings, a vWF preparation can be improved providing additional pro-vWF or pp-vWF as a separate effective protein in the vWF preparation. pp-vWF controls the primary hemostatic activity of the mature vWF and thus reduces the potential thrombotic risk of vWF for e.g. inducing arterial thrombosis as indicated by the prior art.

It was surprisingly found out that a recombinant vWF preparation (rvWF) containing substantial amounts of pp-vWF induces an elevated thrombin generation in vitro. The thrombin generation was measured by an in vitro assay performed with washed vWD platelets in FVIIIC substituted vWD plasma upon addition of FEIBA (factor VIII inhibitor bypassing activity; Austrian patents No 350 726, 368 883 and 398 079) to initiate the activation of prothrombin. When the rvWF preparation contained a predominant amount of pro-vWF and pp-vWF the thrombin generation was substantially increased. The contribution of the pp-vWF to the coagulation-promoting effect of vWF is therefore surprisingly significant.

Since these results imply that the effect of vWF as blood coagulation factor is related to pp-vWF, the pharmaceutical preparation based on the pp-vWF or pro-vWF is applicable in areas wherein vWF has been proposed and even more areas where a coagulation-promoting effect is desired.

The preparation of the pp-vWF or pro-vWF is well known in the art due to many papers relating to expression and properties of vWF or for diagnostic purposes, see e.g. experimental procedures in Isobe et al., Takagi et al. (both 1989 papers) or Leyte et al.. However, there was not yet any individual coagulation promoting activity reported to be associated with vWF and the propeptide region of vWF and therefore not a respective pharmaceutical preparation. Since the pp-vWF is a well defined polypeptide and easily prepared by recombinant DNA-technology, the recombinant way of production is a preferred embodiment for producing the present pharmaceutical preparation. The polypeptide may also be purified or purified further by chromatography, such as by ion exchange chromatography and/or

affinity chromatography using monoclonal antibodies, heparin, collagen, factor VIII protein, or fragments thereof as affinity ligands. It is also possible to separate pp-vWF from contaminating proteins and/or mature vWF by gel filtration.

A preferred embodiment of the present invention is a pharmaceutical preparation essentially consisting of the vWF-propeptide. Thereby the preparation contains purified pp-vWF or pro-vWF to the extent that at least 80%, preferably at least 90%, most preferred more than 95% or about 100% pure pp-vWF or pro-vWF is contained.

Another embodiment of the present invention is a preparation essentially consisting of the pro-vWF containing the vWF-propeptide as a pharmaceutical preparation.

As stated above it is preferred to use recombinantly produced pro-vWF or pp-vWF for the present preparation. (FEBS Letters 351 (1994), 345-348 or Blood 88 (8) 19996, 2951-2958)

The preparations of the present invention preferably contain at least 10 nM pp-vWF, more preferably at least 30 nM, especially more than 50 nM, and/or at least 10 nM pro-vWF, more preferably more than 100 nM, especially more than 250 nM. The effective amount is defined to obtain a pp-vWF level of at least twice the physiologic amount in human plasma. In Blood 88 (8) 1996, 2951 - 2958 it is reported that the molar ratio of the propeptide and vWF concentration is about 0,1 in Normal Plasma. The pp-vWF is considered as a rather abundant protein at a concentration of 5 to 100 nmol/L depending on the state of activation of the endothelium.

If vWF is contained in the preparation besides pro-vWF the molar ratio of the pro-vWF and vWF is at least 10%, which may be measured as U-Antigen detected by a polyclonal antibody preparation directed against vWF antigen. In the preferred preparation according to the invention the molar ratio is even higher, at least 20% or more preferred at least 50%. The most effective preparation according to the invention contains more

than 80% of vWF-Antigen as pro-vWF.

It turned out that a pharmaceutical preparation according to the invention based on pro-vWF is rapidly processed upon administration in vivo. The thus generated pp-vWF is effective in its thrombin potential and coagulation-promoting activity.

In another preferred embodiment the pharmaceutical preparation according to the present invention further contains a hemostasis protein, preferably a blood factor. Preferred embodiments of these blood factors are selected from the group consisting of mature vWF, factor VIII, activated blood coagulation factors, blood factors with FEIB-activity and FEIBA. Any hemostasis protein decreasing the aPTT or PT of normal plasma is a suitable combination with the pp-vWF or pro-vWF.

A combination of the pp-vWF preparation with FVIIIC provides for a pharmaceutical preparation with improved coagulation activity. When the propeptide is in the form of pro-vWF that is complexed to FVIIIC, the pharmaceutical preparation according to the present invention shows additionally improved FVIIIC-stability.

The further combinations in a pharmaceutical preparation according to the invention are provided with a platelet component. Some of the components having binding properties or activity to vWF or pro-vWF or pp-vWF, which are suitable to contribute to the physiological activities, are collagen, platelet glycoprotein, a platelet, fibrinogen, fibrin, heparin, or a derivative thereof.

The pharmaceutical preparation of the present invention may also further contain phospholipids.

The pharmaceutical preparation according to the present invention preferably has been made virus safe by treating for virus inactivation or removal.

The virus inactivation or removal treatment may be performed by any treatment accepted as being efficient. According to

preferred embodiments of the present invention the pharmaceutical composition is treated with tensides and/or heat, e.g. by a heat treatment in the solid state, especially a steam treatment according to EP 0 159 311 or EP 0 519 901 or EP 0 637 451, by a hydrolase treatment according to EP 0 247 998, by a radiation treatment or by a treatment with chemical or chemical/physical methods, e.g. with chaotropic agents, according to WO 94/13329, by a treatment with organic solvents and/or tensides according to EP 0 131 740 or photoinactivation. Nanofiltration also represents a preferred method of depleting viruses within the scope of the present invention.

The pharmaceutical preparation according to the present invention further contains a pharmaceutically acceptable carrier and/or suitable buffer auxiliary preserving and/or stabilizing substances like carbohydrates or salts, or protease inhibitors or cofactors, respectively. The preparation is finally formulated for especially parenteral or topical uses like any known vWF preparation according to the prior art. This may be done by filling it into containers in a form suitable for administration and preferably packing it so as to be storage stable, optionally in the lyophilized or frozen state.

The preparation according to the present invention may be produced both by purification from blood serum or plasma and by a respective expression system. Transgenic animals might as well provide the source of pp-vWF or pro-vWF.

A preparation according to the present invention may also be provided by expression of the pp-vWF or the pro-vWF containing pp-vWF in vivo or ex vivo. Especially suitable for such procedure are cells derived from mammals, in particular human cells, which can be cultured or employed in human gene therapy. Also transformed cells expressing pp-vWF or the pro-vWF as a heterologous protein are a suitable source for obtaining the preparation according to the invention.

A further embodiment according to the present invention is also a pharmaceutical preparation containg a pro-vWF mutant with a

mutation at the cleavage site. Such a mutant has been described by Borchiellini et al. for experimental purposes (Blood 88 (8), 2951-2958 (1996)). The described vWF-Gly 763 has a mutation which provides for a pro-vWF that is unclearable by physiological enzymes. The resistance of the pro-vWF against cleavage leads to the prolonged half-life of the coagulation-promoting activity of the pp-vWF being comprised in the pro-vWF form. Thereby a prolonged action is designed by a specific mutation at the cleavage site.

This specific mutation might by effected by the techniques of Lankhof et al. (Thrombin and Haemostasis 77 (5), 1008 - 13 (1997)) who produced a deletion mutant lacking the A2 domain, which was resistant to proteolysis unless it became sensitive upon unfolding to the molecule.

Other mutant proteins of pp-vWF or pro-vWF that exhibit the properties of the native proteins may also be used for the present preparations. In this case it is preferred to employ an analogue or mutant having at least 80% homology and the function to act as a modified pp-vWF or pro-vWF.

Yet another effect of the present invention is a method for producing a pharmaceutical preparation containing an effective amount of pp-vWF comprising providing a source material containing the vWF propeptide, separating the pp-vWF from the source material and formulating the pp-vWF to a pharmaceutical preparation.

Source material may preferably be blood, serum, blood fractions, colostrum or milk of transgenic animals, or cell culture solutions, especially from cells that have been produced by recombinant DNA-technology. The source material containg pp-vWF preferably contains the pp-vWF in a pro-vWF. Methods and techniques are described in FEBS Letters 351, 345-348 (1994) or Borchiellini et al. supra.

The expression is preferably performed in a way to prevent the processing and maturation of vWF to obtain the pro-vWF. This may

be effected by the omission or inhibition of processing enzymes. The inhibition of processing enzymes like furin or PACE or the multimerase as described in A 770/96 and 769/96 prevents the premature processing of pro-vWF to vWF. On the other hand the pp-vWF might be expressed as a separate protein or obtained upon cleavage and processing of the pro-vWF in vitro.

Yet another preferred embodiment of the present invention is conducting the method by providing a source material containing the pro-vWF as a mutant pro-vWF with a mutation at the cleavage site of the pp-vWF, such as an amino acid change at 763 like pro-vWF-Gly 763.

Alternatively, the pharmaceutical preparation may be produced in the presence of an inhibitor inhibiting the cleavage of the pp-vWF from the pro-vWF. Examples for such inhibitors are antibodies against the cleavage site or a binding peptide directed against the cleavage site or inhibitor of processing enzyme.

As stated above, the preparation and separation steps of pp-vWF are well-known in the art due to various reports of the experiments conducted with pp-vWF (see Isobe et al., Tagaki et al., Leyte et al.).

Of course, the method according to the present invention preferably exhibits a treatment for inactivating or removing viruses, since the pp-vWF is a biological protein and in a form which is administered to humans.

The invention further provides pp-vWF and/or pro-vWF for use as a medicine. The effective dose to elevate the pp-vWF level in vivo to at least twice the physiological amount may be provided by administering the pp-vWF or the pro-vWF once or several times a day. Due to the rather short half-life of the pp-vWF in vivo it might be necessary to administer the protein frequently during the acute disorder.

Yet another aspect of the present invention is the use of pp-vWF

and/or pro-vWF containing the pp-vWF for the preparation of a pharmaceutical composition for treating a patient at a risk of blood coagulation disorders, such as vWD, hemophilia (f.e. phenotypic hemophilia, hemophilia A and factor VIII inhibitors).

The effective dosage of the preparation when applied will vary depending on the respective syndrom and preferably should be chosen after determination of the blood levels of the critical blood factors or risk for thrombosis in the patient. The optimum dosage also depends on whether or not the parenteral, preferably intravenous, subcutaneous or intramuscular adiministration is to be effected in bolus form or as a depot. By using a suitable carrier material such as liposomes a peroral administration is feasible. It also depends on whether it is to be applied systemically and/or locally at the site of the blood coagulation disorder.

Therefore, the invention also provides for a method of treating a patient at a risk of blood coagulation disorders comprising administering to said patient an effective amount of vWF-propeptide or pro-vWF. Preferably, a patient suffering from vWD, phenotypic hemophilia, hemophilia A or factor VIII inhibitors is treated according to the invention.

Due to the positive properties pp-vWF or pro-vWF exhibit when combined with preparations with a risk for arterial thrombosis, such as vWF-preparations, it is another aspect of the present invention to use pp-vWF or pro-vWF to reduce thrombosis risk in vWF-preparations. Thereby the potential exaggeration of arterial thrombus formation is effectively down-modulated, whereas the intrinsic and extrinsic blood coagulation is promoted in case of a coagulation deficiency.

In particular the compatibility of a vWF preparation is ameliorated and improved by the addition of and combination with the pp-vWF or pro-vWF in effective amounts. Because of the controlling function of the vWF propeptide it further contributes to the treatment and prevention of adverse reactions of endogenous and exogenous vWF, particularly elevated vWF

levels in patients associated with thrombotic thrombocytopenic purpura, Henoch Schönlein purpura, preclampsia, neonatal thrombocytopenia or hemolytic uremic syndrome, myocardial infarction or a poor outcome following arterial surgery.

The present invention will be explained in more detail by way of the following examples and drawing figures to which, however, it shall not be restricted.

Fig.1 shows the effect of pro-vWF on the thrombin generation in plasma in the presence of platelets,

Fig.2 shows the dose dependent effect of pro-vWF on the thrombin generation in plasma in the presence of platelets,

Figs.3a and 3b show the comparison of the in vivo effect of pro-vWF and plasma derived vWF in a dog.

Examples:

1. The effect of provWF an ppvWF on the thrombin generation in plasma in the presence of platelets.

Severe vWD plasma (George King Bio-Medical Inc., USA) which was previously reconstituted with 1 U/ml FVIIIC (Recombinate, Baxter, USA) (200 µl) was incubated with 50 µl washed platelets from a severe vWD patient (Type III) in the presence of 0.1 U/ml FEIBA (Immuno, Austria) and 16 mM $CaCl_2$. Alternatively FVIIa could also be used as an activator, preferably in a final concentration of 0.2 µg/ml. Subsamples of 10 µl were withdrawn at time intervals, and added to 300 µl chromogenic substrate for thrombin (D-cyclohexyl-gly-L-Ala-L-Arg -pNA; Immuno, Austria) containing 3 mM EDTA to stop any further reactions. The reaction was stopped by the addition of 100 µl of 75 % (v/v) acetic acid, and the absorbance, which is the function of the thrombin concentration, was measured at 405 nm.

Two different vWF preparations (containing lower and higher amounts of provWF and propeptide) were added to the factor VIII

reconstituted plasma samples in a final concentration of 1 Risto U/ml, and thrombin generation was followed. (1 Risto U/ml = the ristocetin cofactor activity of the vWF in normal plasma). Thus the plasma samples contained in the case of the preparation with the low provWF and low propeptide 0.24 nM provWF and 0.19 nM propeptide, while the other one contained 34 nM provWF and 4 nM propeptide, respectively.

The results are depicted on Figure 1.

It is clear from the curves, that albeit both preparations increased the rate of thrombin generation, the high provWF and high propeptide containing product had a stronger effect and produced the enhanced thrombin generation.

2. The effect of provWF on the thrombin generation in plasma in the presence of platelets.

The effect of a recombinant vWF preparation, which contained more then 90% provWF of the total vWF antigen on the thrombin generation was investigated in the system described by the Example 1. Washed platelets from an other severe vWD patient (Type III) and the isolated plasma sample of the same patient, reconstituted with 1 U/ml FVIIIC were used in the experiments. Recombinant provWF of 2 and 5 vWF-Ag U/ml (1 Ag U = the vWF antigen amount in 1 ml normal plasma) respectively, were added to the plasma samples and thrombin generation was compared with that of in the absence of vWF. Figure 2 shows, that above a threshold of 2 vWF-Ag U/ml an increased thrombin generation was observed.

Example 3. Comparison of the in vivo effect of a high provWF containing recombinant and a plasma derived vWF preparation.

A vWF deficient dog (vWF antigen below the detection limit, and factor VIII activity about 50 % of the normal) was anesthetized and infused with 35 Risto U/ml of the recombinant vWF used in the example 2, containing more then 90 % of provWF. Prior to the infusion and 15, 30, 40 minutes, 1, 2, 3, 6, 24, 48, 72, an 95

hours post infusion plasma samples were taken. 95 hours later a plasma derived vWF preparation (Haemate HS - Behringwerke, Marburg, Germany) was added, and plasma samples were taken again at the same intervals after the infusion, as before. This plasma derived vWF preparation further contained Factor VIII:C, but no provWF and no ppvWF. The plasma samples were analyzed for total vWF antigen (Asserachrom ELISA, Boehringer), provWF and propeptide antigen (according to Borchiellini at al Blood 88, 2951, 1996), as well as for the thrombin generation potential, as described in Example 1. The thrombin potential is defined as the maximum thrombin concentration measured as described in Example 1.

Figure 3 shows the correlations of the various parameters, expressed as percent of maximum, regarding the initial values as zero.

Thrombin potential increased in parallel with the increase of propeptide after the treatment with a recombinant provWF preparation. ELISA results showed, that a few percent of provWF remained in the circulation after 15 minutes, and it could no longer be detected (data not shown), but a significant increase in the propeptide and vWF was observed. In contrast, no propeptide and also no substantial thrombin potential was observed in the dog after the plasma derived vWF infusion, despite of the vWF antigen level increase.

Claims:

1. Pharmaceutical preparation for treating blood coagulation disorders comprising an effective amount of vWF propeptide.

2. Preparation according to claim 1 essentially consisting of vWF propeptide.

3. Preparation according to claim 1 comprising pro-vWF containing the vWF propeptide.

4. Preparation according to claim 3, wherein the pro-vWF is a recombinant pro-vWF.

5. Preparation according to claim 1 to 4 which further contains a hemostasis protein, preferably a blood factor.

6. Preparation according to claim 5, wherein the blood factor is selected from the group consisting of mature vWF, factor VIII, activated blood coagulation factors, blood factors with FEIB-activity and FEIBA.

7. Preparation according to claim 6, wherein the pro-vWF is complexed to factor VIII.

8. Preparation according to claim 1 to 7 which further contains a platelet component, preferably at least one of a collagen, a platelet glycoprotein, a platelet, fibrinogen, fibrin, heparin, or a derivative thereof.

9. Preparation according to claim 1 to 8 which further contains phospholipids.

10. Preparation according to claim 1 to 9 which is treated for virus inactivation or virus removal.

11. Preparation according to claim 1 to 10 which further contains a pharmaceutically acceptable carrier.

12. Preparation according to claim 1 to 11, wherein the vWF propeptide is recombinant vWF propeptide.

13. A method for producing a pharmaceutical preparation containing an effective amount of vWF propeptide comprising providing a source material containing the vWF propeptide, separating the vWF propeptide from the source material and formulating the vWF propeptide to a pharmaceutical preparation.

14. A method according to claim 13, wherein the vWF propeptide is treated for inactivating or removing viruses.

15. A method accoding to claim 13 or 14, wherein the source material is plasma or a plasma fraction.

16. A method according to claim 13 or 14, wherein the source material is obtained from a cell culture.

17. A method according to claim 13, wherein the vWF propeptide is produced by recombinant DNA technology.

18. A method according to claim 13 to 17, wherein the vWF propeptide is contained in a pro-vWF.

19. A method according to claim 18, wherein the pro-vWF is a mutant pro-vWF with a mutation at the cleavage site of the vWF propeptide.

20. A method according to claim 13 to 19, wherein the pharmaceutical preparation is produced in the presence of an inhibitor which inhibits the cleavage of the vWF propeptide from the pro-vWF.

21. A method according to claim 13 to 20, wherein the vWF propeptide is separated by chromatography, preferably by affinity chromatography, from the source material.

22. A method according to claim 21, wherein the affinity chromatography employs carrier materials with ligands specific

for the vWF propeptide.

23. vWF-propeptide as a medicine.

24. pro-vWF containing vWF propeptide as medicine.

25. Use of vWF propeptide and/or pro-vWF containing the vWF propeptide for the preparation of a pharmaceutical composition for treating a patient at a risk of blood coagulation disorders.

26. Use of vWF propeptide and/or pro-vWF composition for the preparation of a pharmaceutical composition for the treatment of vWD inhibitors.

27. Use of pp-vWF or pro-vWF for improving the compatibility of pharmaceutical vWF-preparations.

28. Use of pp-vWF or pro-VWF for the preparation of a pharmaceutical composition for the treatment or prevention of adverse effects of endogenous or exogenous vWF, particularly elevated vWF levels associated with thrombotic thrombocytopenic purpura, Henoch-Schönlein Purpura, preclampsia, neonatal thrombocytopenia or hemolytic-uremic syndrome, myocardial infarction or poor outcome following arterial surgery.

29. Use of vWF propeptide and/or pro-vWF composition for the preparation of a pharmaceutical composition for the treatment of hemophilia.

30. Use of vWF propeptide and/or pro-vWF composition according to claim 29 for the treatment of phenotypic hemophilia, hemophilia A and factor VIII inhibitors.

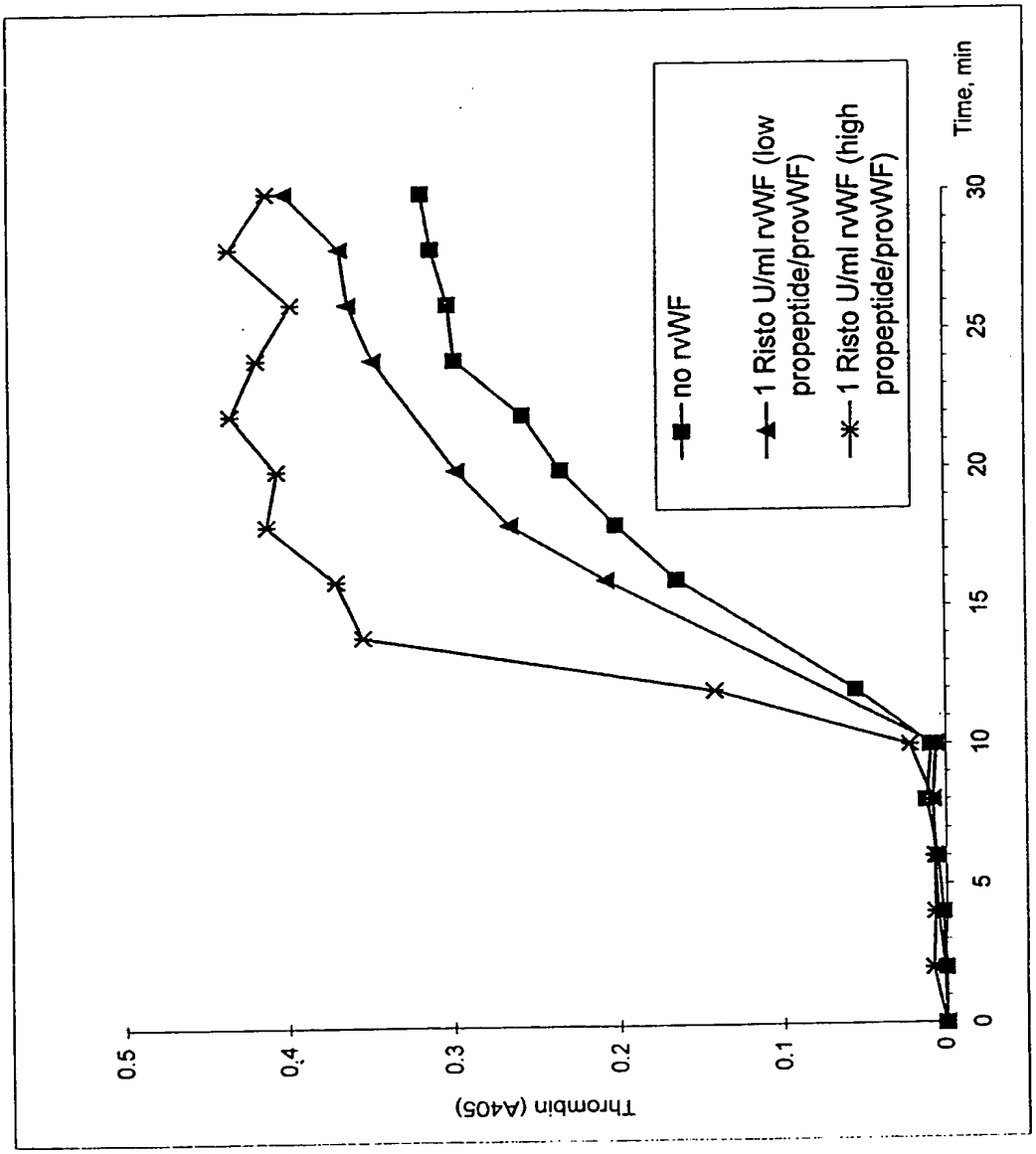

Fig 1: The effect of provWF on the thrombin generation in plasma in the presence of platelets.

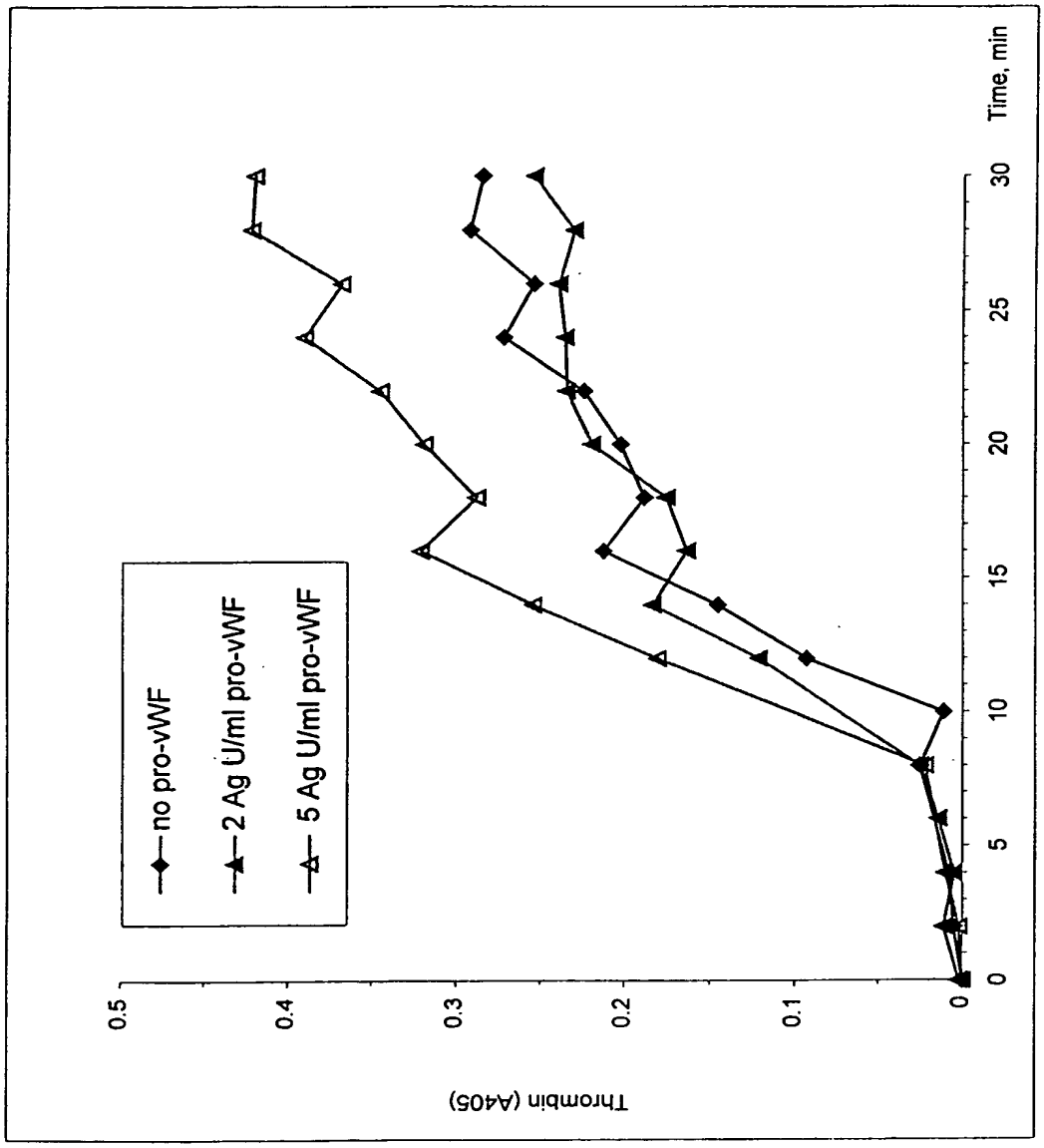

Fig 2: Dose dependent effect of provWF on the thrombin generation in plasma in the presence of platelets.

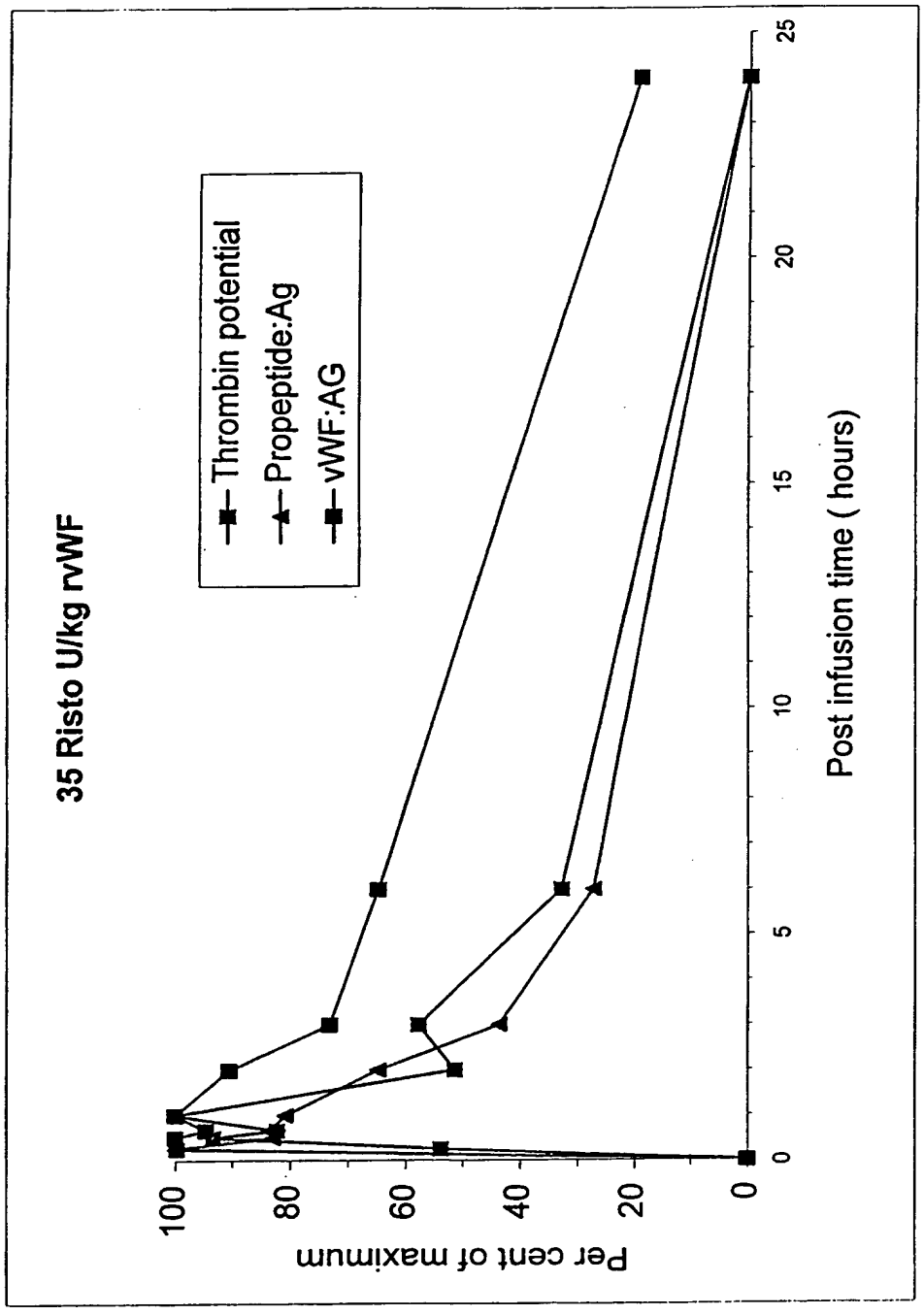

Fig. 3a Comparison of the in vivo effect a recombinant vWF (pro-vWF) and plasma derived vWF preparation in a dog

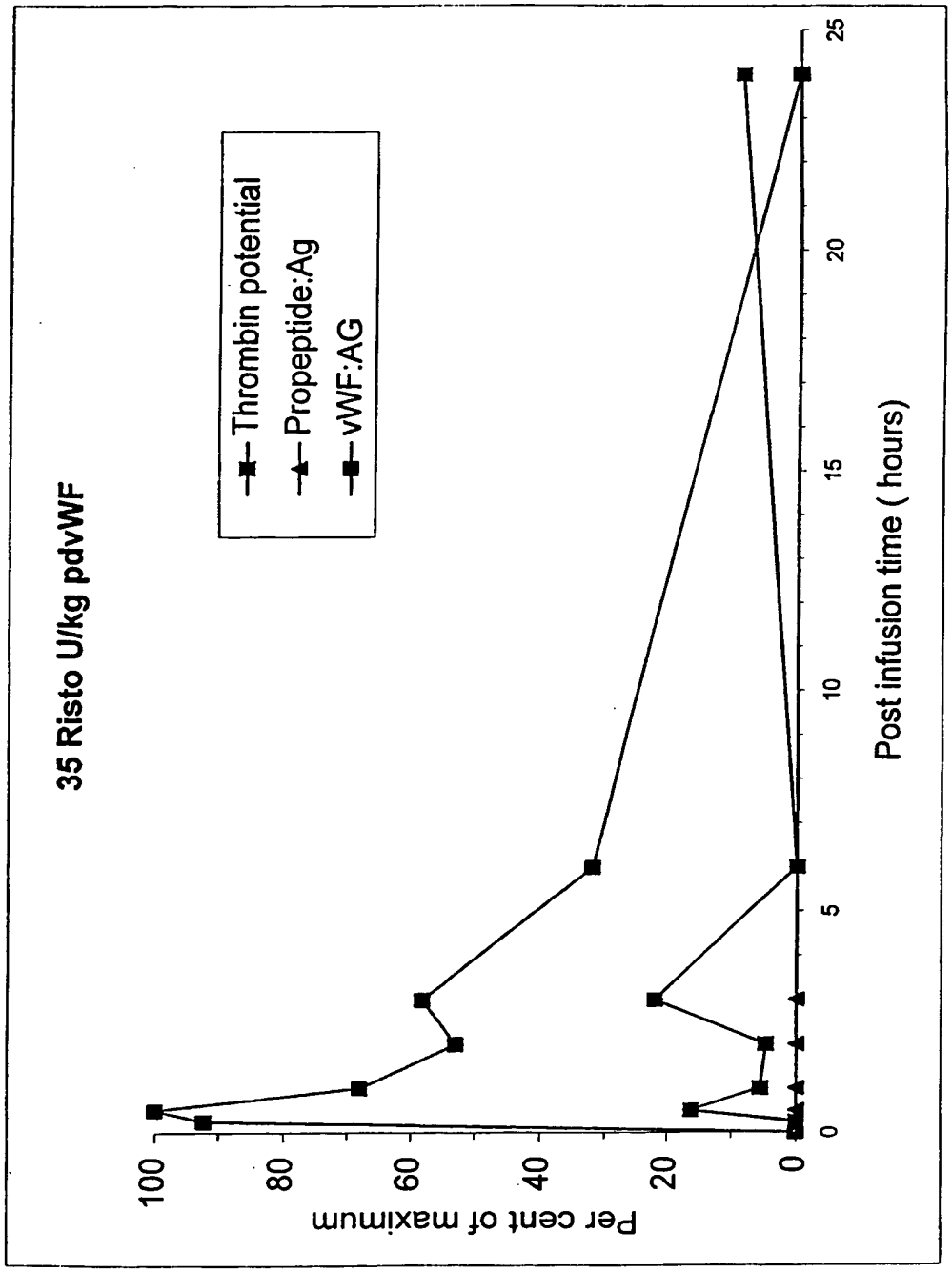
35 Risto U/kg pdvWF
Thrombin potential
Propeptide:Ag
vWF:AG
Per cent of maximum
0
20
40
60
80
100
0
5
10
15
20
25
Post infusion time (hours)

Fig.3b

ENT COOPERATION TRE

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION OF ELECTION

(PCT Rule 61.2)

To:

United States Patent and Trademark Office
(Box PCT)
Crystal Plaza 2
Washington, DC 20231
ÉTATS-UNIS D'AMÉRIQUE

in its capacity as elected Office

Date of mailing (day/month/year) 12 January 1999 (12.01.99)	
International application No. PCT/EP98/03090	**Applicant's or agent's file reference** R 34083
International filing date (day/month/year) 26 May 1998 (26.05.98)	**Priority date** (day/month/year) 28 May 1997 (28.05.97)
Applicant SCHWARZ, Hans-Peter et al	

1. The designated Office is hereby notified of its election made:

[X] in the demand filed with the International Preliminary Examining Authority on:

17 December 1998 (17.12.98)

[ ] in a notice effecting later election filed with the International Bureau on:

2. The election [X] was

[ ] was not

made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

The International Bureau of WIPO **34, chemin des Colombettes** **1211 Geneva 20, Switzerland**	Authorized officer Nicola Wolff
Facsimile No.: (41-22) 740.14.35	Telephone No.: (41-22) 338.83.38

Form PCT/IB/331 (July 1992)

2423168

PATENT COOPERATION TREATY

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION OF THE RECORDING OF A CHANGE

(PCT Rule 92bis.1 and Administrative Instructions, Section 422)

To:

SONN, Helmut
Riemergasse 14
A-1010 Vienna
AUTRICHE

Date of mailing (day/month/year)	
01 October 1999 (01.10.99)	
Applicant's or agent's file reference R 34083	**IMPORTANT NOTIFICATION**
International application No. PCT/EP98/03090	**International filing date** (day/month/year) 26 May 1998 (26.05.98)

1. The following indications appeared on record concerning:

[X] the applicant [ ] the inventor [ ] the agent [ ] the common representative

Name and Address	State of Nationality	State of Residence
IMMUNO AKTIENGESELLSCHAFT Industriestrasse 67 A-1221 Vienna Austria	AT	AT
	Telephone No.	
	Facsimile No.	
	Teleprinter No.	

2. The International Bureau hereby notifies the applicant that the following change has been recorded concerning:

[ ] the person [X] the name [ ] the address [ ] the nationality [ ] the residence

Name and Address	State of Nationality	State of Residence
BAXTER AKTIENGESELLSCHAFT Industriestrasse 67 A-1221 Vienna Austria	AT	AT
	Telephone No.	
	Facsimile No.	
	Teleprinter No.	

3. Further observations, if necessary:

4. A copy of this notification has been sent to:

[X] the receiving Office
[ ] the International Searching Authority
[ ] the International Preliminary Examining Authority
[ ] the designated Offices concerned
[X] the elected Offices concerned
[ ] other:

The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland	Authorized officer Yolaine CUSSAC
Facsimile No.: (41-22) 740.14.35	Telephone No.: (41-22) 338.83.38

TENT COOPERATION TREATY

From the INTERNATIONAL SEARCHING AUTHORITY

PCT

NOTIFICATION OF TRANSMITTAL OF THE INTERNATIONAL SEARCH REPORT OR THE DECLARATION

(PCT Rule 44.1)

To:
SONN, PAWLOY, WEINZINGER, PAWLOY
und ALGE
Riemergasse 14
A-1010 Wien
AUSTRIA

EINGELANGT
09. Okt. 1998
FRIST: 7.12.98

Date of mailing (day/month/year): 07/10/1998

Applicant's or agent's file reference	FOR FURTHER ACTION See paragraphs 1 and 4 below
R 34083	
International application No. PCT/EP 98/03090	International filing date (day/month/year) 26/05/1998

Applicant

IMMUNO AKTIENGESELLSCHAFT et al.

1. [X] The applicant is hereby notified that the International Search Report has been established and is transmitted herewith.

Filing of amendments and statement under Article 19
The applicant is entitled, if he so wishes, to amend the claims of the International Application (see Rule 46):

When? The time limit for filing such amendments is normally 2 months from the date of transmittal of the International Search Report; however, for more details, see the notes on the accompanying sheet.

Where? Directly to the International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland
Fascimile No.: (41-22) 740.14.35

For more detailed instructions, see the notes on the accompanying sheet.

2. [ ] The applicant is hereby notified that no International Search Report will be established and that the declaration under Article 17(2)(a) to that effect is transmitted herewith.

3. [ ] **With regard to the protest** against payment of (an) additional fee(s) under Rule 40.2, the applicant is notified that:

[ ] the protest together with the decision thereon has been transmitted to the International Bureau together with the applicants's request to forward the texts of both the protest and the decision thereon to the designated Offices.

[ ] no decision has been made yet on the protest; the applicant will be notified as soon as a decision is made.

4. **Further action(s):** The applicant is reminded of the following:

Shortly after **18 months** from the priority date, the international application will be published by the International Bureau. If the applicant wishes to avoid or postpone publication, a notice of withdrawal of the international application, or of the priority claim, must reach the International Bureau as provided in Rules 90*bis*.1 and 90*bis*.3, respectively, before the completion of the technical preparations for international publication.

Within **19 months** from the priority date, a demand for international preliminary examination must be filed if the applicant wishes to postpone the entry into the national phase until 30 months from the priority date (in some Offices even later).

Within **20 months** from the priority date, the applicant must perform the prescribed acts for entry into the national phase before all designated Offices which have not been elected in the demand or in a later election within 19 months from the priority date or could not be elected because they are not bound by Chapter II.

Name and mailing address of the International Searching Authority	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL-2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Dominique Parijs

Form PCT/ISA/220 (January 1994)

NOTES TO FORM PCT/ISA/220

These Notes are intended to give the basic instructions concerning the filing of amendments under article 19. The Notes are based on the requirements of the Patent Cooperation Treaty, the Regulations and the Administrative Instructions under that Treaty. In case of discrepancy between these Notes and those requirements, the latter are applicable. For more detailed information, see also the PCT Applicant's Guide, a publication of WIPO.

In these Notes, "Article", "Rule", and "Section" refer to the provisions of the PCT, the PCT Regulations and the PCT Administrative Instructions respectively.

INSTRUCTIONS CONCERNING AMENDMENTS UNDER ARTICLE 19

The applicant has, after having received the international search report, one opportunity to amend the claims of the international application. It should however be emphasized that, since all parts of the international application (claims, description and drawings) may be amended during the international preliminary examination procedure, there is usually no need to file amendments of the claims under Article 19 except where, e.g. the applicant wants the latter to be published for the purposes of provisional protection or has another reason for amending the claims before international publication. Furthermore, it should be emphasized that provisional protection is available in some States only.

What parts of the international application may be amended?

Under Article 19, only the claims may be amended.

During the international phase, the claims may also be amended (or further amended) under Article 34 before the International Preliminary Examining Authority. The description and drawings may only be amended under Article 34 before the International Examining Authority.

Upon entry into the national phase, all parts of the international application may be amended under Article 28 or, where applicable, Article 41.

When? Within 2 months from the date of transmittal of the international search report or 16 months from the priority date, whichever time limit expires later. It should be noted, however, that the amendments will be considered as having been received on time if they are received by the International Bureau after the expiration of the applicable time limit but before the completion of the technical preparations for international publication (Rule 46.1).

Where not to file the amendments?

The amendments may only be filed with the International Bureau and not with the receiving Office or the International Searching Authority (Rule 46.2).

Where a demand for international preliminary examination has been/is filed, see below.

How? Either by cancelling one or more entire claims, by adding one or more new claims or by amending the text of one or more of the claims as filed.

A replacement sheet must be submitted for each sheet of the claims which, on account of an amendment or amendments, differs from the sheet originally filed.

All the claims appearing on a replacement sheet must be numbered in Arabic numerals. Where a claim is cancelled, no renumbering of the other claims is required. In all cases where claims are renumbered, they must be renumbered consecutively (Administrative Instructions, Section 205(b)).

The amendments must be made in the language in which the international application is to be published.

What documents must/may accompany the amendments?

Letter (Section 205(b)):

The amendments must be submitted with a letter.

The letter will not be published with the international application and the amended claims. It should not be confused with the "Statement under Article 19(1)" (see below, under "Statement under Article 19(1)").

The letter must be in English or French, at the choice of the applicant. However, if the language of the international application is English, the letter must be in English; if the language of the international application is French, the letter must be in French.

The letter must indicate the differences between the claims as filed and the claims as amended. It must, in particular, indicate, in connection with each claim appearing in the international application (it being understood that identical indications concerning several claims may be grouped),whether

(i) the claim is unchanged;

(ii) the claim is cancelled;

(iii) the claim is new;

(iv) the claim replaces one or more claims as filed;

(v) the claim is the result of the division of a claim as filed.

The following examples illustrate the manner in which amendments must be explained in the accompanying letter:

1. [Where originally there were 48 claims and after amendment of some claims there are 51]:
"Claims 1 to 29, 31, 32, 34, 35, 37 to 48 replaced by amended claims bearing the same numbers; claims 30, 33 and 36 unchanged; new claims 49 to 51 added."

2. [Where originally there were 15 claims and after amendment of all claims there are 11]:
"Claims 1 to 15 replaced by amended claims 1 to 11."

3. [Where originally there were 14 claims and the amendments consist in cancelling some claims and in adding new claims]:
"Claims 1 to 6 and 14 unchanged; claims 7 to 13 cancelled; new claims 15, 16 and 17 added." or
"Claims 7 to 13 cancelled; new claims 15, 16 and 17 added; all other claims unchanged."

4. [Where various kinds of amendments are made]:
"Claims 1-10 unchanged; claims 11 to 13, 18 and 19 cancelled; claims 14, 15 and 16 replaced by amended claim 14; claim 17 subdivided into amended claims 15, 16 and 17; new claims 20 and 21 added."

"Statement under article 19(1)" (Rule 46.4)

The amendments may be accompanied by a statement explaining the amendments and indicating any impact that such amendments might have on the description and the drawings (which cannot be amended under Article 19(1)).

The statement will be published with the international application and the amended claims.

It must be in the language in which the international appplication is to be published.

It must be brief, not exceeding 500 words if in English or if translated into English.

It should not be confused with and does not replace the letter indicating the differences between the claims as filed and as amended. It must be filed on a separate sheet and must be identified as such by a heading, preferably by using the words "Statement under Article 19(1)."

It may not contain any disparaging comments on the international search report or the relevance of citations contained in that report. Reference to citations, relevant to a given claim, contained in the international search report may be made only in connection with an amendment of that claim.

Consequence if a demand for international preliminary examination has already been filed

If, at the time of filing any amendments under Article 19, a demand for international preliminary examination has already been submitted, the applicant must preferably, at the same time of filing the amendments with the International Bureau, also file a copy of such amendments with the International Preliminary Examining Authority (see Rule 62.2(a), first sentence).

Consequence with regard to translation of the international application for entry into the national phase

The applicant's attention is drawn to the fact that, where upon entry into the national phase, a translation of the claims as amended under Article 19 may have to be furnished to the designated/elected Offices, instead of, or in addition to, the translation of the claims as filed.

For further details on the requirements of each designated/elected Office, see Volume II of the PCT Applicant's Guide.

TENT COOPERATION TREAT

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference	FOR FURTHER ACTION	see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.
R 34083		
International application No.	International filing date *(day/month/year)*	(Earliest) Priority Date *(day/month/year)*
PCT/EP 98/ 03090	26/05/1998	28/05/1997
Applicant		
IMMUNO AKTIENGESELLSCHAFT et al.		

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 3 sheets.

[X] It is also accompanied by a copy of each prior art document cited in this report.

1. [ ] **Certain claims were found unsearchable** (see Box I).

2. [ ] **Unity of invention is lacking** (see Box II).

3. [ ] The international application contains disclosure of a **nucleotide and/or amino acid sequence listing** and the international search was carried out on the basis of the sequence listing
   - [ ] filed with the international application.
   - [ ] furnished by the applicant separately from the international application,
     - [ ] but not accompanied by a statement to the effect that it did not include matter going beyond the disclosure in the international application as filed.
   - [ ] Transcribed by this Authority

4. With regard to the **title,**
   - [X] the text is approved as submitted by the applicant
   - [ ] the text has been established by this Authority to read as follows:

5. With regard to the **abstract,**
   - [X] the text is approved as submitted by the applicant
   - [ ] the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this International Search Report, submit comments to this Authority.

6. The figure of the **drawings** to be published with the abstract is:
   Figure No. 1
   - [X] as suggested by the applicant.
   - [ ] because the applicant failed to suggest a figure.
   - [ ] because this figure better characterizes the invention.
   - [ ] None of the figures.

INTERNATIONAL SEARCH REPORT

[redacted]ational Application No
[redacted]CT/EP 98/03090

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61K38/37

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	PATENT ABSTRACTS OF JAPAN vol. 096, no. 004, 30 April 1996 & JP 07 330797 A (SUMITOMO METAL IND LTD), 19 December 1995 see abstract ---	1-30
A	FISCHER B E ET AL: "Structural analysis of recombinant von Willebrand factor produced at industrial scale fermentation of transformed CHO cells co-expressing recombinant furin." FEBS LETTERS, (1995 NOV 20) 375 (3) 259-62. JOURNAL CODE: EUH. ISSN: 0014-5793., XP002078561 Netherlands see page 259 see abstract --- -/--	1-30

[X] Further documents are listed in the continuation of box C.

[ ] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
24 September 1998	07/10/1998

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Sitch, W

Form PCT/ISA/210 (second sheet) (July 1992)

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
A	FISCHER ET AL: "Structural analysis of recombinant von Willebrand factor: identification of hetero- and homo-dimers" FEBS LETTERS, vol. 351, 1994, pages 345-348, XP002078562 cited in the application see page 345 see abstract see page 348, paragraph 2 ---	1-30
A	TAKAGI ET AL: "Inhibition of Platelet-Collagen Interaction by Propolypeptide of von Willebrand Factor" THE JOURNAL OF BIOLOGICAL CHEMISTRY, vol. 264, 1989, pages 6017-6020, XP002078563 cited in the application see page 6017 see abstract ---	1-30
A	ISOBE ET AL: "Propolypeptide of von Willebrand Factor Is a Novel Ligand for Very Late Antigen-4 Integrin" THE JOURNAL OF BIOLOGICAL CHEMISTRY, vol. 272, 28 March 1997, pages 8447-8453, XP002078564 cited in the application see page 8447 see abstract ---	1-30
A	LEYTE ET AL: "The pro-polypeptide of von Willebrand Factor is required for the formation of a functional Factor VIII-binding site on mature von Willebrand Factor" BIOCHEMICAL JOURNAL, vol. 274, 1991, pages 257-261, XP002078565 cited in the application see page 257 see abstract -----	1-30

WO 98/53848
PCT/EP98/03090

PATENT COOPERATION TREATY

From the INTERNATIONAL BUREAU

PCT

NOTICE INFORMING THE APPLICANT OF THE COMMUNICATION OF THE INTERNATIONAL APPLICATION TO THE DESIGNATED OFFICES

(PCT Rule 47.1(c), first sentence)

To:
SONN, Helmut
Riemergasse 14
A-1010 Vienna
AUTRICHE

Date of mailing (day/month/year) 03 December 1998 (03.12.98)	
Applicant's or agent's file reference R 34083	**IMPORTANT NOTICE**

International application No.	**International filing date** (day/month/year)	**Priority date** (day/month/year)
PCT/EP98/03090	26 May 1998 (26.05.98)	28 May 1997 (28.05.97)

Applicant
IMMUNO AKTIENGESELLSCHAFT et al

1. Notice is hereby given that the International Bureau has communicated, as provided in Article 20, the international application to the following designated Offices on the date indicated above as the date of mailing of this Notice:
   AU,BR,CA,CN,EP,IL,JP,KP,KR,PL,US

   In accordance with Rule 47.1(c), third sentence, those Offices will accept the present Notice as conclusive evidence that the communication of the international application has duly taken place on the date of mailing indicated above and no copy of the international application is required to be furnished by the applicant to the designated Office(s).

2. The following designated Offices have waived the requirement for such a communication at this time:
   AL,AM,AP,AT,AZ,BA,BB,BG,BY,CH,CU,CZ,DE,DK,EA,EE,ES,FI,GB,GE,GH,GM,GW,HU,ID,IS,KE,
   KG,KZ,LC,LK,LR,LS,LT,LU,LV,MD,MG,MK,MN,MW,MX,NO,NZ,OA,PT,RO,RU,SD,SE,SG,SI,SK,SL,
   TJ,TM,TR,TT,UA,UG,UZ,VN,YU,ZW
   The communication will be made to those Offices only upon their request. Furthermore, those Offices do not require the applicant to furnish a copy of the international application (Rule 49.1(a-bis)).

3. Enclosed with this Notice is a copy of the international application as published by the International Bureau on
   03 December 1998 (03.12.98) under No. WO 98/53848

REMINDER REGARDING CHAPTER II (Article 31(2)(a) and Rule 54.2)

If the applicant wishes to postpone entry into the national phase until 30 months (or later in some Offices) from the priority date, **a demand for international preliminary examination** must be filed with the competent International Preliminary Examining Authority before the expiration of 19 months from the priority date.

It is the applicant's sole responsibility to monitor the 19-month time limit.

Note that only an applicant who is a national or resident of a PCT Contracting State which is bound by Chapter II has the right to file a demand for international preliminary examination.

REMINDER REGARDING ENTRY INTO THE NATIONAL PHASE (Article 22 or 39(1))

If the applicant wishes to proceed with the international application in the **national phase**, he must, within 20 months or 30 months, or later in some Offices, perform the acts referred to therein before each designated or elected Office.

For further important information on the time limits and acts to be performed for entering the national phase, see the Annex to Form PCT/IB/301 (Notification of Receipt of Record Copy) and Volume II of the PCT Applicant's Guide.

The International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland

Facsimile No. (41-22) 740.14.35

Authorized officer
J. Zahra

Telephone No. (41-22) 338.83.38

C ntinuati n f Form PCT/IB/308

NOTICE INFORMING THE APPLICANT OF THE COMMUNICATION OF THE INTERNATIONAL APPLICATION TO THE DESIGNATED OFFICES

Dat f mailing (day/month/year) 03 December 1998 (03.12.98)	IMPORTANT NOTICE
Applicant's or agent's file reference R 34083	International application No. PCT/EP98/03090

The applicant is hereby notified that, at the time of establishment of this Notice, the time limit under Rule 46.1 for making amendments under Article 19 has not yet expired and the International Bureau had received neither such amendments nor a declaration that the applicant does not wish to make amendments.

PATENT COOPERATION TREATY

From the INTERNATIONAL BUREAU

PCT

INFORMATION CONCERNING ELECTED OFFICES NOTIFIED OF THEIR ELECTION

(PCT Rule 61.3)

To:

EINGELANGT
18. Jan. 1999
FRIST: .....

SONN, Helmut
Riemergasse 14
A-1010 Vienna
AUTRICHE

Date of mailing (day/month/year) 12 January 1999 (12.01.99)	
Applicant's or agent's file reference R 34083	**IMPORTANT INFORMATION**

International application No.	**International filing date** (day/month/year)	**Priority date** (day/month/year)
PCT/EP98/03090	26 May 1998 (26.05.98)	28 May 1997 (28.05.97)

Applicant
IMMUNO AKTIENGESELLSCHAFT et al

1. The applicant is hereby informed that the International Bureau has, according to Article 31(7), notified each of the following Offices of its election:

   AP :GH,GM,KE,LS,MW,SD,SZ,UG,ZW
   EP :AT,BE,CH,CY,DE,DK,ES,FI,FR,GB,GR,IE,IT,LU,MC,NL,PT,SE
   National :AU,BG,BR,CA,CN,CZ,DE,GB,IL,JP,KP,KR,MN,NO,NZ,PL,RO,RU,SE,SK,US,VN

2. The following Offices have waived the requirement for the notification of their election; the notification will be sent to them by the International Bureau only upon their request:

   EA :AM,AZ,BY,KG,KZ,MD,RU,TJ,TM
   OA :BF,BJ,CF,CG,CI,CM,GA,GN,ML,MR,NE,SN,TD,TG
   National :AL,AM,AT,AZ,BA,BB,BY,CH,CU,DK,EE,ES,FI,GE,GH,GM,GW,HU,ID,IS,KE,KG,KZ,LC,LK,LR,LS,LT,LU,LV,MD,MG,MK,MW,MX,PT,SD,SG,SI,SL,TJ,TM,TR,TT,UA,UG,UZ,YU,ZW

3. The applicant is reminded that he must enter the "national phase" **before the expiration of 30 months from the priority date** before each of the Offices listed above. This must be done by paying the national fee(s) and furnishing , if prescribed, a translation of the international application (Article 39(1)(a)), as well as, where applicable, by furnishing a translation of any annexes of the international preliminary examination report (Article 36(3)(b) and Rule 74.1).

   Some offices have fixed time limits expiring later than the above-mentioned time limit. For detailed information about the applicable time limits and the acts to be performed upon entry into the national phase before a particular Office, see Volume II of the PCT Applicant's Guide.

   The entry into the European regional phase is postponed **until 31 months from the priority date** for all States designated for the purposes of obtaining a European patent.

The International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland

Facsimile No. (41-22) 740.14.35

Authorized officer:
Nicola Wolff

Telephone No. (41-22) 338.83.38

PCT

REQUEST

The undersigned requests that the present international application be processed according to the Patent Cooperation Treaty.

For receiving Office use only

International Application No. PCT/EP 98/03090

International Filing Date (26.05.98) 26 MAY 1998

EUROPEAN PATENT OFFICE
PCT INTERNATIONAL APPLICATION

Name of receiving Office and "PCT International Application"

Applicant's or agent's file reference *(if desired) (12 characters maximum)* R 34083

Box No. I TITLE OF INVENTION

Pharmaceutical preparation comprising vWF propeptide

Box No. II APPLICANT

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (i.e. country) of residence if no State of residence is indicated below.)*

IMMUNO AKTIENGESELLSCHAFT

Industriestraße 67
A-1221 Vienna, Austria

☐ This person is also inventor.

Telephone No.

Facsimile No.

Teleprinter No.

State *(i.e. country)* of nationality: AT

State *(i.e. country)* of residence: AT

This person is applicant for the purposes of: ☐ all designated States ☒ all designated States except the United States of America ☐ the United States of America only ☐ the States indicated in the Supplemental Box

Box No. III FURTHER APPLICANT(S) AND/OR (FURTHER) INVENTOR(S)

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (i.e. country) of residence if no State of residence is indicated below.)*

SCHWARZ, Hans-Peter

Schindlergasse 32
A-1180 Vienna, Austria

This person is:

☐ applicant only

☒ applicant and inventor

☐ inventor only *(If this check-box is marked, do not fill in below.)*

State *(i.e. country)* of nationality: AT

State *(i.e. country)* of residence: AT

This person is applicant for the purposes of: ☐ all designated States ☐ all designated States except the United States of America ☒ the United States of America only ☐ the States indicated in the Supplemental Box

☒ Further applicants and/or (further) inventors are indicated on a continuation sheet.

Box No. IV AGENT OR COMMON REPRESENTATIVE; OR ADDRESS FOR CORRESPONDENCE

The person identified below is hereby/has been appointed to act on behalf of the applicant(s) before the competent International Authorities as: ☒ agent ☐ common representative

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)*

SONN, Helmut, PAWLOY, Heinrich, WEINZINGER Arnulf, PAWLOY, Peter, ALGE, Daniel

Riemergasse 14
A-1010 Vienna, Austria

Telephone No. +43 1 512 84 05

Facsimile No. + 43 1 512 98 05

Teleprinter No.

☐ Mark this check-box where no agent or common representative is/has been appointed and the space above is used instead to indicate a special address to which correspondence should be sent.

Continuation of Box No. III **FURTHER APPLICANTS AND/OR (FURTHER) INVENTORS**

If none of the following sub-boxes is used, this sheet is not to be included in the request.

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (i.e. country) of residence if no State of residence is indicated below.)*

VARADI, Katalin

Othellogasse 1/6/2
A-1230 Vienna, Austria

This person is:
- ☐ applicant only
- ☒ applicant and inventor
- ☐ inventor only *(If this check-box is marked, do not fill in below.)*

State *(i.e. country)* of nationality: HU

State *(i.e. country)* of residence: AT

This person is applicant for the purposes of:
- ☐ all designated States
- ☐ all designated States except the United States of America
- ☒ the United States of America only
- ☐ the States indicated in the Supplemental Box

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (i.e. country) of residence if no State of residence is indicated below.)*

TURECEK, Peter

Hauptstraße 59g
Weidling
A-3400 Klosterneuburg, Austria

This person is:
- ☐ applicant only
- ☒ applicant and inventor
- ☐ inventor only *(If this check-box is marked, do not fill in below.)*

State *(i.e. country)* of nationality: AT

State *(i.e. country)* of residence: AT

This person is applicant for the purposes of:
- ☐ all designated States
- ☐ all designated States except the United States of America
- ☒ the United States of America only
- ☐ the States indicated in the Supplemental Box

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (i.e. country) of residence if no State of residence is indicated below.)*

HEMKER, Hendrik Coenraad

Tongersestraat 41
NL-6211 LM Maastricht, Netherlands

This person is:
- ☐ applicant only
- ☒ applicant and inventor
- ☐ inventor only *(If this check-box is marked, do not fill in below.)*

State *(i.e. country)* of nationality: NL

State *(i.e. country)* of residence: NL

This person is applicant for the purposes of:
- ☐ all designated States
- ☐ all designated States except the United States of America
- ☒ the United States of America only
- ☐ the States indicated in the Supplemental Box

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (i.e. country) of residence if no State of residence is indicated below.)*

BEGUIN, Suzette Lucette

Akerstraat 12 B
NL-6221 CL Maastricht, Netherlands

This person is:
- ☐ applicant only
- ☒ applicant and inventor
- ☐ inventor only *(If this check-box is marked, do not fill in below.)*

State *(i.e. country)* of nationality: FR

State *(i.e. country)* of residence: NL

This person is applicant for the purposes of:
- ☐ all designated States
- ☐ all designated States except the United States of America
- ☒ the United States of America only
- ☐ the States indicated in the Supplemental Box

☐ Further applicants and/or (further) inventors are indicated on another continuation sheet

Box No.V DESIGNATION OF STATES

The following designations are hereby made under Rule 4.9(a) *(mark the applicable check-boxes; at least one must be marked)*:

Regional Patent

- ☒ AP **ARIPO Patent:** GH Ghana, GM Gambia, KE Kenya, LS Lesotho, MW Malawi, SD Sudan, SZ Swaziland, UG Uganda, ZW Zimbabwe, and any other State which is a Contracting State of the Harare Protocol and of the PCT
- ☒ EA **Eurasian Patent:** AM Armenia, AZ Azerbaijan, BY Belarus, KG Kyrgyzstan, KZ Kazakhstan, MD Republic of Moldova, RU Russian Federation, TJ Tajikistan, TM Turkmenistan, and any other State which is a Contracting State of the Eurasian Patent Convention and of the PCT
- ☒ EP **European Patent:** AT Austria, BE Belgium, CH and LI Switzerland and Liechtenstein, DE Germany, DK Denmark, ES Spain, FI Finland, FR France, GB United Kingdom, GR Greece, IE Ireland, IT Italy, LU Luxembourg, MC Monaco, NL Netherlands, PT Portugal, SE Sweden, and any other State which is a Contracting State of the European Patent Convention and of the PCT CY Cyprus
- ☒ OA **OAPI Patent:** BF Burkina Faso, BJ Benin, CF Central African Republic, CG Congo, CI Côte d'Ivoire, CM Cameroon, GA Gabon, GN Guinea, ML Mali, MR Mauritania, NE Niger, SN Senegal, TD Chad, TG Togo, and any other State which is a member State of OAPI and a Contracting State of the PCT *(if other kind of protection or treatment desired, specify on dotted line)* .....

National Patent *(if other kind of protection or treatment desired, specify on dotted line)*:

- ☒ AL Albania
- ☒ AM Armenia
- ☒ AT Austria
- ☒ AU Australia
- ☒ AZ Azerbaijan
- ☒ BA Bosnia and Herzegovina
- ☒ BB Barbados
- ☒ BG Bulgaria
- ☒ BR Brazil
- ☒ BY Belarus
- ☒ CA Canada
- ☒ CH and LI Switzerland and Liechtenstein
- ☒ CN China
- ☒ CU Cuba
- ☒ CZ Czech Republic
- ☒ DE Germany
- ☒ DK Denmark
- ☒ EE Estonia
- ☒ ES Spain
- ☒ FI Finland
- ☒ GB United Kingdom
- ☒ GE Georgia
- ☒ GH Ghana
- ☒ GM Gambia
- ☒ GW Guinea-Bissau
- ☒ HU Hungary
- ☒ ID Indonesia
- ☒ IL Israel
- ☒ IS Iceland
- ☒ JP Japan
- ☒ KE Kenya
- ☒ KG Kyrgyzstan
- ☒ KP Democratic People's Republic of Korea
- ☒ KR Republic of Korea
- ☒ KZ Kazakhstan
- ☒ LC Saint Lucia
- ☒ LK Sri Lanka
- ☒ LR Liberia
- ☒ LS Lesotho
- ☒ LT Lithuania
- ☒ LU Luxembourg
- ☒ LV Latvia
- ☒ MD Republic of Moldova
- ☒ MG Madagascar
- ☒ MK The former Yugoslav Republic of Macedonia
- ☒ MN Mongolia
- ☒ MW Malawi
- ☒ MX Mexico
- ☒ NO Norway
- ☒ NZ New Zealand
- ☒ PL Poland
- ☒ PT Portugal
- ☒ RO Romania
- ☒ RU Russian Federation
- ☒ SD Sudan
- ☒ SE Sweden
- ☒ SG Singapore
- ☒ SI Slovenia
- ☒ SK Slovakia
- ☒ SL Sierra Leone
- ☒ TJ Tajikistan
- ☒ TM Turkmenistan
- ☒ TR Turkey
- ☒ TT Trinidad and Tobago
- ☒ UA Ukraine
- ☒ UG Uganda
- ☒ US United States of America
- ☒ UZ Uzbekistan
- ☒ VN Viet Nam
- ☒ YU Yugoslavia
- ☒ ZW Zimbabwe

Check-boxes reserved for designating States (for the purposes of a national patent) which have become party to the PCT after issuance of this sheet:

- ☐ .....
- ☐ .....
- ☐ .....

In addition to the designations made above, the applicant also makes under Rule 4.9(b) all designations which would be permitted under the PCT except the designation(s) of _____.

The applicant declares that those additional designations are subject to confirmation and that any designation which is not confirmed before the expiration of 15 months from the priority date is to be regarded as withdrawn by the applicant at the expiration of that time limit. *(Confirmation of a designation consists of the filing of a notice specifying that designation and the payment of the designation and confirmation fees. Confirmation must reach the receiving Office within the 15-month time limit.)*

Box No. VI PRIORITY CLAIM Further priority claims are indicated in the Supplemental Box ☐

The priority of the following earlier application(s) is hereby claimed:

Country *(in which, or for which, the application was filed)*	Filing Date *(day/month/year)*	Application No.	Office of filing *(only for regional or international application)*
item (1) AT	28 May 1997 (28.05.97)	A 917/97	
item (2)			
item (3)			

Mark the following check-box if the certified copy of the earlier application is to be issued by the Office which for the purposes of the present international application is the receiving Office (a fee may be required):

☐ The receiving Office is hereby requested to prepare and transmit to the International Bureau a certified copy of the earlier application(s) identified above as item(s) : _____

Box No. VII INTERNATIONAL SEARCHING AUTHORITY

Ch ice of International Searching Authority (ISA) *(If two or more International Searching Authorities are competent to carry out the international search, indicate the Authority chosen; the two-letter code may be used):* ISA /_____

Earlier search *Fill in where a search (international, international-type or other) by the International Searching Authority has already been carried out or requested and the Authority is now requested to base the international search, to the extent possible, on the results of that earlier search. Identify such search or request either by reference to the relevant application (or the translation thereof) or by reference to the search request:*

Country (or regional Office): Date *(day/month/year)*: Number:

B x No. VIII CHECK LIST

This international application contains the following number of sheets:

1. request	4	sheets
2. description	13	sheets
3. claims	3	sheets
4. abstract	1	sheets
5. drawings	4	sheets
Total	25	sheets

This international application is accompanied by the item(s) marked below:

1. [X] separate signed power of attorney 5
2. ☐ copy of general power of attorney
3. ☐ statement explaining lack of signature
4. [X] priority document(s) *identified in Box No. VI as item(s):*
5. [X] fee calculation sheet
6. ☐ separate indications concerning deposited microorganisms
7. ☐ nucleotide and/or amino acid sequence listing (diskette)
8. ☐ other *(specify)*:

Figure No. 1 of the drawings (if any) should accompany the abstract when it is published.

Box No. IX SIGNATURE OF APPLICANT OR AGENT

Next to each signature, indicate the name of the person signing and the capacity in which the person signs (if such capacity is not obvious from reading the request).

Renate MOLDAN, Head of the Patent Administration Department

IMMUNO AKTIENGESELLSCHAFT

Daniel ALGE
Patent Attorney

For receiving Office use only

1. Date of actual receipt of the purported international application: 26 MAY 1998 (26.05.98)	2. Drawings: ☒ received: ☐ not received:
3. Corrected date of actual receipt due to later but timely received papers or drawings completing the purported international application:	
4. Date of timely receipt of the required corrections under PCT Article 11(2):	
5. International Searching Authority specified by the applicant: ISA /	6. ☐ Transmittal of search copy delayed until search fee is paid

For International Bureau use only

Date of receipt of the record copy by the International Bureau:

PATENT COOPERATION TREATY

From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

To:

SONN, PAWLOY, WEINZINGER, PAWLOY
und ALGE
Riemergasse 14
A-1010 Wien
AUTRICHE

EINGELANGT
16. Aug. 1999
FRIST: .....

PCT

NOTIFICATION OF TRANSMITTAL OF THE INTERNATIONAL PRELIMINARY EXAMINATION REPORT
(PCT Rule 71.1)

Date of mailing *(day/month/year)*	11. 08. 99
Applicant's or agent's file reference R 34083	**IMPORTANT NOTIFICATION**

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/EP98/03090	26/05/1998	28/05/1997

Applicant
IMMUNO AKTIENGESELLSCHAFT et al.

1. The applicant is hereby notified that this International Preliminary Examining Authority transmits herewith the international preliminary examination report and its annexes, if any, established on the international application.

2. A copy of the report and its annexes, if any, is being transmitted to the International Bureau for communication to all the elected Offices.

3. Where required by any of the elected Offices, the International Bureau will prepare an English translation of the report (but not of any annexes) and will transmit such translation to those Offices.

4. **REMINDER**

The applicant must enter the national phase before each elected Office by performing certain acts (filing translations and paying national fees) within 30 months from the priority date (or later in some Offices) (Article 39(1)) (see also the reminder sent by the International Bureau with Form PCT/IB/301).

Where a translation of the international application must be furnished to an elected Office, that translation must contain a translation of any annexes to the international preliminary examination report. It is the applicant's responsibility to prepare and furnish such translation directly to each elected Office concerned.

For further details on the applicable time limits and requirements of the elected Offices, see Volume II of the PCT Applicant's Guide.

Name and mailing address of the IPEA/	Authorized officer
European Patent Office D-80298 Munich Tel. (+49-89) 2399-0 Tx: 523656 epmu d Fax: (+49-89) 2399-4465	THORNTON, J Tel.(+49-89) 2399-8072

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
R 34083		
International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/EP98/03090	26/05/1998	28/05/1997
International Patent Classification (IPC) or national classification and IPC		
A61K38/37		
Applicant		
IMMUNO AKTIENGESELLSCHAFT et al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 6 sheets, including this cover sheet.

   ☐ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the report
   - II ☐ Priority
   - III ☐ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations suporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☒ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
17/12/1998	11.08.99
Name and mailing address of the international preliminary examining authority:	Authorized officer
European Patent Office D-80298 Munich Tel. (+49-89) 2399-0 Tx: 523656 epmu d Fax: (+49-89) 2399-4465	Schnack, A Telephone No. (+49-89) 2399 8149

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/EP98/03090

I. Basis of the report

1. This report has been drawn on the basis of (*substitute sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to the report since they do not contain amendments.*):

Description, pages:

1-13 as originally filed

Claims, No.:

1-30 as originally filed

Drawings, sheets:

1/4-4/4 as originally filed

2. The amendments have resulted in the cancellation of:

☐ the description, pages:
☐ the claims, Nos.:
☐ the drawings, sheets:

3. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

4. Additional observations, if necessary:

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-30
	No:	Claims	none
Inventive step (IS)	Yes:	Claims	none
	No:	Claims	1-30
Industrial applicability (IA)	Yes:	Claims	1-30
	No:	Claims	none

2. Citations and explanations

see separate sheet

VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

see separate sheet

Reference is made to the following documents:

D1: The Journal of Biological Chemistry, vol. 264, no. 11, pp. 6017-6020, 1988

Section V
V.1. Novelty

It appears that the subject matter of present claims 1-30 is novel in the sense of Article 33(1) and (2) PCT with respect to the cited references, because all of those references describe in-vitro experimental studies and as such do not disclose pharmaceutical preparations containing pro-vWF or pp-vWF. Neither does it appear that the cited references directly disclose the use of these peptides for use as therapeutics.

V.2. Inventive step
Objections under Article 33(3) PCT:

D1 discloses in-vitro studies performed in order to investigate the physiological role of pp-vWF. It is concluded that pp-vWF has a strong affinity to collagen and that it inhibits collagen-induced aggregation of human platelets. This suggests that pp-vWF and vWF may have opposing effects on hemostasis, (see D1, the abstract). D1 further concludes that it seems possible that pp-vWF has a unique function in hemostasis independent of mature vWF, since it is known to be released from platelets upon activation by thrombin, collagen and ADP. It is stated that since pp-vWF inactivates collagen upon short incubation, released pp-vWF should immediately bind to exposed collagen layer at the site of vessel wall injury and may prevent further adhesion of platelets to subendothelium, (see D1, page 6018, 2. col., lines 2-10 from bottom).

Preparations comprising vWF and other blood coagulation factors are known in the art, (cf. present application, page 2, paragraph 4). One disadvantage associated with these coagulation-promoting preparations is the risk of arterial thrombosis, (cf. present application, page 10, 4. paragraph). Thus, the objective technical problem to be solve can be formulated as the provision of an improved vWF-preparation, the improvement consisting in a reduced risk of arterial thrombosis. The technical teaching forming basis for a proper selection of an agent which reduces the risk of arterial thrombosis appears

to be disclosed in D1; namely that pp-vWF inhibits the collagen-induced platelets aggregation, (see D1, the abstract). Thus, it appears that the skilled man would find it obvious that pp-vWF can solve the problem of risk of arterial thrombosis associated with known coagulation-promoting preparations, irrespective of the fact that the present application has provided novel evidence that pp-vWF and pro-vWF enhance the intrinsic blood coagulation activity through an induction of thrombin formation, (cf. present application, page 4, second paragraph). Based on this argument, it appears that the subject matter of present claims 1, 2, 4-17, 21-23 and 25-30 lacks an inventive step over D1.

Moreover, it appears to be known in the art that pro-vWF is cleaved in-vivo so as to obtain pp-vWF, (cf. present description, page 8, lines 3-9 from bottom). Therefore, it does not appear to require inventive skills to conclude that pro-vWF also has a therapeutic potential, because it is cleaved in-vivo to obtain the known active peptide, pp-vWF. Therefore also present claims 3, 18-20 and 24 appears to lack an inventive step over D1 in combination with the general state of the art.

V.3. Industrial applicability

The subject matter of present claims 1-30 fulfils the requirements for industrial applicability laid down in Article 33(4) PCT.

Section VIII

Objections under Article 5 and 6 PCT:

The subject matter of present claim 9 does not appear to be supported by the description.

Present claim 9 is unclear, because the mutant is not defined. Furthermore it is not from the wording of the claim clear for which purpose the mutation is introduced. Moreover, also the description does not appear to define the present mutants sufficiently clear in that only one example is mentioned, (cf. present application, page 7, line 2 from bottom - page 8, paragraph three).

Present claims 5, 8, 9 and 11 refer inter alia to claim 2. This dependency appears to be

unclear since claim 2 is directed to a preparation which essentially consists of pp-vWF, whereas claim 5 is broader in that is contains further ingredients.

Claim 27 appears to be unclear, because it is not clear which compatibility it refers to. Normally incompatibility exists between at least two items, but it is not clear from the claim what that could be. Moreover, it appears that the subject matter of present claim 27 is not supported by the description.

Present dependent claim 19 casts doubt to which peptides are actually claimed in the present application, since claim 19 relates to mutant pro-vWF, which does not appear to be embraced by terms pp-vWF or pro-vWF according to independent claim 13. Besides, all other claims relate to pp-vWF or pro-vWF and not to derivatives or mutants of those peptides. This introduces unclarity, because it is not possible to determine which peptides are intended to be embraced by the present claims.

The subject matter of present claim 20 appears to be unclear and insufficiently disclosed by the description, in that no explicit examples nor reference to such are given of suitable inhibitors.

PATENT COOPERATION TREATY

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION OF THE RECORDING OF A CHANGE

(PCT Rule 92bis.1 and Administrative Instructions, Section 422)

To:

SONN, Helmut
Riemergasse 14
A-1010 Vienna
AUTRICHE

EINGELANGT
11. Okt. 1999
FRIST.

Date of mailing (day/month/year) 01 October 1999 (01.10.99)	
Applicant's or agent's file reference R 34083	**IMPORTANT NOTIFICATION**
International application No. PCT/EP98/03090	International filing date (day/month/year) 26 May 1998 (26.05.98)

1. The following indications appeared on record concerning:

[X] the applicant [ ] the inventor [ ] the agent [ ] the common representative

Name and Address
IMMUNO AKTIENGESELLSCHAFT
Industriestrasse 67
A-1221 Vienna
Austria

State of Nationality: AT
State of Residence: AT
Telephone No.:
Facsimile No.:
Teleprinter No.:

2. The International Bureau hereby notifies the applicant that the following change has been recorded concerning:

[ ] the person [X] the name [ ] the address [ ] the nationality [ ] the residence

Name and Address
BAXTER AKTIENGESELLSCHAFT
Industriestrasse 67
A-1221 Vienna
Austria

State of Nationality: AT
State of Residence: AT
Telephone No.:
Facsimile No.:
Teleprinter No.:

3. Further observations, if necessary:

4. A copy of this notification has been sent to:

[X] the receiving Office
[ ] the Internati nal Searching Authority
[ ] the International Preliminary Examining Auth rity
[ ] the designated Offices concerned
[X] the elected Offices concerned
[ ] ther:

The International Bureau of WIPO
34, chemin des Col mbettes
1211 Geneva 20, Switzerland
Facsimile N .: (41-22) 740.14.35

Authorized fficer
Y laine CUSSAC
Telephone No.: (41-22) 338.83.38

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